REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the following remarks.

Claims 284-286 and 288 are currently pending in the application. Claims 275-283, 287 and 289-296 have been canceled without prejudice. Claims 284-286 and 288 have not been amended and no new matter has been added to the specification or the claims.

More particularly, in the currently outstanding Official Action:

1. Claims 284-286 and 288 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

> The Examiner states, "The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.
>
> The claims are drawn to a combination of dosage amounts comprising hyaluronic acid (HA) having molecular weight of less than 750,000 daltons. Claims 284-286 are generic combinations wherein the first dosage amount comprises HA and an NSAID and/or a chemotherapeutic agent and, optionally, an antioxidant. The second dosage amount comprises HA and an anti-cancer drug and/or drug suitable for use to treat cancer. Claim 288 is drawn to a specific combination wherein the first dosage amount comprises HA (as sodium hyaluronate) and diclofenac sodium and/or novantrone and, optionally, vitamin C. The second dosage amount comprises HA (as sodium hyaluronate) and novantrone.
>
> Throughout the specification, there are laundry lists of suggested pharmaceutical agents, but the examiner finds no particular support for either of the generic or specific combinations of therapeutic agents in the claims.".

Applicants respectfully disagree. The specification of the present application provides dozens of examples from pages 36-58 of the various agents for administration regimens as directed to in the claims. In order to assist the Examiner in correlating the disclosure (particularly the Examples) with the wording of the claims, Applicants provide Table 1 below which clearly indicates the treatment regimen for each patient and the applicable claims (see right-hand column).

Thus, an example of the Claim 284 combination dosage is clearly provided in the treatment regime recited for Patent 1 who received DMSO a chemotherapeutic agent [component 1(i)], hyaluronic acid [component 1(ii)] followed by hyaluronic acid [component 2(i)] and indomethacin [component 2(ii)].

Applicants respectfully request reconsideration. For a discussion on the differences between chemotherapeutics drugs, anti-cancer drugs and drugs suitable to treat cancer, please see below.

Table 1: Patient treatment details

Patient 1	Radiation –resistant Squamous tumour metstatsized to liver	33	DMSO Phloretin solubilised in N methyl glucamine with DMSO Adriamycin Carboplatinum Methotrexate HA 10-60mg for each drug Follow-up indomethacin and HA	✓ Applicable to Claim 284 & 286
Patient 2	Chemotherapy resistant melanoma	33	Phloretin solubilised in N methyl glucamine DMSO HA 10-60mg for each drug Hyperthermia Carbopainum Metyl CCNU Methotrexate Follow-up indomethacin HA Phloretin	✓ Applicable to Claim 284 & 286
Patient 3	Cancer of gallbladder	34	Hyperthermia Systemic chemotherapy Phloretin DMSO	✓ Applicable to Claim 284 & 286
Patient 4	Colon cancer metstatsized to liver	35	Hyperthermia Systemic chemotherapy Phloretin solubilised in N methyl glucamine DMSO HA	✓ Applicable to Claim 284 & 286
Patient 5	Bladder cancer	35	Phloretin solubilised in N methyl glucamine with DMSO Carboplatinum Methotrexate HA 10-60mg for each drug Hyperthermia	✓ Applicable to Claim 284 & 286
Patient 6	Liver cancer non-responsive to chemotherapy or radiotherapy	36	Vinblastine Mitomycin c 5-fluorouracil Leukovorin Carboplatin methotrexate HA Phloretin	✓ Applicable to Claim 284 & 286
Patient 7	Breast cancer resistant to chemotherapy, radiation, hyperthermia	40	Methotrexate 5-fluorouracil Vinblastine Mitomycin c Carboplatin Phloretin Leukovorin HA Phloretin	✓ Applicable to Claim 284 & 286
Patient 8	Lung cancer resistant to chemotherapy	43	Bleomycin Indomethecin HA	✓ Applicable to Claim 284, 285 & 286
Patient 9	Gastric cancer	44	Hyperthermia Phloretin 5-fluorouracil methotrexate mitomycin C novotrone DMSO HA	✓ Applicable to Claim 284, 286 & 288

Patient 10	Hepatoma	45	Not stated merely claims "chemotherapy and carrier/penetrating molecule, HA"	✓ Applicable to Claim 284 & 286
Patient 11	Breast cancer	45	Hyperthermia Chemotherapy HA Tamoxifen Indomethicin	✓ Applicable to Claim 284, 285 & 286
Patient 11A	Sarcoma of the uterus	45	Hyperthermia Methotrexate Phloretin Interferon HA Vitamin c Indomthecin	✓ Applicable to Claim 284, 285 & 286
Patient 11B	Melanoma	46	Interferon Hyperthermia CCNU Carboplatin Methotrexate Phloretin HA	✓ Applicable to Claim 284 & 286
Patient 12	Infected site		Anti-bacterial agents HA	Not applicable
Patient 13	Infected site		Anti-bacterial agents HA	
Patient 14	Infected site		Anti-bacterial agents HA	
Patient 15	Infected site		Anti-bacterial agents HA	
Patient number not given	Canker sores		Interferon HA	
Patient number not given	psoriasis		methotrexate HA	Not applicable
Patient number not given	Herpes simplex virus		Nonoxynol-9 HA	Not applicable
Patient 17	Stomach cancer metastasized to liver		5-fluorouracil mitomycin C novantrone Vitamin C HA	✓ Applicable to Claim 284, 285, 286 & 288
Patient 18	Colon cancer that metastasized to liver	50	Phloretin Hyperthermia HA Vitamin C Indomethicin	✓ Applicable to Claim 284 & 286
Patient 19	Lung cancer	50	Vitamin C Indomethicin HA Toradol	✓ Applicable to Claim 284, 285 & 286
Patient 20	colon cancer	51	Methotrexate Oncostatin Vitamin C Indomethicin HA	✓ Applicable to Claim 284, 285 & 286
Patient 21	Cancer of the uterus	51	Phloretin Vitamin C Indomethicin HA	✓ Applicable to Claim 284, 285 & 286
Patient 22	Adenocarcinoma	51	Phloretin DMSO Vitamin C Naproxen HA	✓ Applicable to Claim 284 & 286

Patient 23	Esophageal cancer	52	Phloretin Indomethicin Hyperthermia Vitamin C HA	✓ Applicable to Claim 284, 285 & 286
Patient 24	Pancreatic cancer	52	Hyperthermia DMSO Chemotherapy Vitamin c HA	✓ Applicable to Claim 284, 285 & 286
Patient 25	Pancreatic cancer	53	5-fluorouracil mitomycin C HA Hyperthermia Indomtheicin Vitamin c	✓ Applicable to Claim 284, 285 & 286
Patient 26	Infectious mononucleosis		Vitamin c HA	Not applicable
Patient 27	Cancer not mentioned which type	53	Hyperthermia Phloretin Vitamin c Indomethicin 5-fluorouracil	✓ Applicable to Claim 284, 285 & 286
Patient 28	Ovarian cancer	57	Furosemide HA	✓ Applicable to Claim 284 & 286

2. Claims 284-286 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

> The Examiner states, "Claim 284, at line 11, recites "a chemotherapeutic agent" and at line 16, recites "an anti-cancer drug" or "drug suitable for use to treat cancer." Typically, a drug used to treat cancer is thought to be a "chemotherapeutic agent." However, the instant specification refers to "chemotherapeutic agents" and "anti-cancer drugs" in the alternative. It is not clear is one is a sub-set of the other or if each is a non-overlapping group. Furthermore, the examiner finds no explanation regarding the difference between "an anti-cancer drug" and "a drug suitable for use to treat cancer." Due to these uncertainties, on of ordinary skill would not be apprised of the metes and bounds of the claims. The claims are thereby rendered vague and indefinite.".

Applicants respectfully disagree. The terms "chemotherapeutic drug", "anti-cancer drug" and "drug suitable to treat cancer" are, in fact, different in scope and that a person skilled in the relevant art would clearly understand the definition of each, such as the following:

• ***Chemotherapeutic drug*** *is* considered a therapeutic that inhibits the development of an infecting host be it a bacteria or cancer cell.

• ***Anti-cancer drug*** **is** defined as a molecule that can be administered both *in vitro* and *in vivo* where there is substantial death of cancer cells without being lethal to the host.

• ***Drug suitable to treat cancer*** encompasses molecules that may not be cytotoxic but could be used in combination with cytotoxic agents to produce a slowing, regression or eradication of cancer.

As seen from the above definitions there are areas of overlap in the scope of the terms but each is distinct. Therefore, these terms are not synonymous and it is incorrect to merely substitute one for the other. For example, interferon can be used to treat cancer but is not an anti-cancer agent or chemotherapeutic agent.

Other examples include:

Chemotherapeutic /drug suitable to treat cancer

Dimethyl sulfoxide (DMSO) - This is an organic solvent which was initially used in the pharmaceutical industry as a penetration enhancer for topically applied drugs (Barry (2004) Advances in Drug Delivery Rev. 56: 603-618) where side-effects of irritation were always observed (Olver (1988) J Clin Oncol. 6: 1732-1735). Due to the irritant properties of DMSO, it has not and still is not being used as an intravenous or intra-tumoural drug penetrant (Murdoch (1982) Can J Hasp Pharm. 35: 79-85) or enhancer. Dimethyl sulfoxide does in fact demonstrate anti-cancer properties where it has been demonstrated to be anti-angiogenic (Koizumi (2003) Biol Pharm Bull. 1295-1298), have anti-inflammatory effects, alter the biodistrubution of intravenous chemotherapeutic drugs thereby exerting a synergistic effect in anti-cancer treatment regimens (Thuning (1983) CA Ann NY Acad Sci 411: 150-160) and act as a scavenger of reactive oxygen

species (ROS) which are prevalent in tumours whereby the inactivation of these ROS can enhance the apoptosis of tumour cells (Barry (2001) Vet Hum Toxicol 43; 228-231).

Phloretin - This is an inhibitor of glucose transport where it has been extensively used in the treatment of cancer (Kobari (1999) Biosci Biotechnol Biochem 63:719-728) as a means of enhancing tumour cell apoptosis by regulating potassium channels in the cell membrane (Kraft (2003) Pflugers Arch 446: 248-255), once again indicating that Phloretin is not merely a routinely used additive in the treatment of cancer but does exert its own anti-cancer effects. Oncostatin - This compound is a member of the interleukin-6 family which functions as an inhibitor of tumour growth (Sivko (2004) J Cell Biochem. 93: p 830-84), once again it is not a chemotherapeutic agent or common additive to cancer treatment regimens.

- Interferon - This was also used in the treatment of the patients. Interferon is well established as an immune stimulator that can enhance the body's' recognition and removal of tumour cells, this is not a normal additive to chemotherapy regimens.

Anti-Oxidant

Vitamin C - Vitamin C is known as an anti-oxidant , but it is well documented that Vitamin C can be used in the treatment and prevention of cancer where it can demonstrate e therapeutic effect by stimulating collagen formation which inhibits cancer progression and metastasis and stimulates the immune system where clearance of tumour mass is increased (Plead (1998) Altern Med. Rev 3: 174-186 and Riordan (2004) PR Health Sci 23: 115-118). Clinical trials on intravenous Vitamin C as a sole agent have been conducted (Mantovani (2004) Cancer Epidemiol Biomarkers Rev. 13: 1651-1659) once again demonstrating that Vitamin C does have the ability to exert anti-cancer effects and contribute significantly to the efficacy of cancer treatment regimens.

Non-Steroidal Anti-inflammatory/ a drug suitable for use to treat cancer

Indomethicin - This drug is classified as a non-steroidal anti-inflammatory which has been demonstrated in to exert an apoptotic property and inhibitory effects on the activity and/or expression of matrix metalloproteinases and in doing so exert anti-cancer effects (Mirshafiey (2004) Med Sci Monit. 10:PI105-109).

In view thereof, Applicants respectfully request the rejection should be withdrawn.

3. Claims 284-286 are rejected under 35 U.S.C. 103(a) as being unpatentable over DELLA VALLE et al (US 5,166,331) in view of FRANCHI et al (Rec. Prog. Med., 1989 – abstract) and WOOD (US 4,912,136).

> The Examiner states, "DELLA VALLE teaches that HA (including salts) having molecular weight of about 500-730 kD has utility for preparing intra-articular injection dosages for the treatment of joint disorders. See abstract; col 14 and lines 10-27. The reference specifically suggests that the HA is a suitable vehicle for a variety of pharmaceutical agents, including NSAIDs and chemotherapeutics. The reference does not exemplify the particularly recited dosages forms.
>
> FRANCHI teaches the treatment of rheumatoid arthritis (RA) by intra-articular administration of methotrexate and orgotein (an antioxidant). See abstract.
>
> WOOD teaches the use of an NSAID for conditions requiring immunosuppressive therapy, such as RA. See abstract and table in col 3.
>
> It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare dosage amounts comprising any combination of these pharmaceutical agents having utility for the treatment of a joint disorder, such as RA. One of ordinary skill would reasonably expect success because DELLA VALLE had suggested the preparation of such compositions. It would be within the scope of the practitioner to prepare dosages with any combination, as needed, for the treatment of a patient in need, for the additive effects.".

Applicants respectfully disagree. Della Valle *et al.* (US Patent No. 5,166,331) relate to fractions of hyaluronic acid (HA) having pharmaceutical applications without inflammatory activity. It also provides for a fraction of HA which is useful for stimulating wound healing. The claims of the invention relate to topical HA applications and methods of treating ophthalmological conditions. In contrast, the above-identified invention is directed to the treatment of cancer comprising HA together with components such as, i.e. DMSO, indomethacin, phlorelin, Vitamin C and a chemotherapeutic agent.

Franchi *et al.* (Rec. Prog. Med, 1989) recite intrarticular methotrexate in the treatment of rheumatoid arthritis. Franchi *et al.* does not mention HA or the treatment of cancer or Wood *et al.* (US Patent No. 4,912,136) relate to the use of fenclofenac (2-(2,4-dichloro-phenoxphenylacetic) acid as an immunosuppressant drug. There is no reference to HA in the claims.

Thus, Applicants submit that the present invention is not obvious in light of the three prior art documents. In view thereof, the rejection should be withdrawn.

In summary, reconsideration of this application and the allowance of Claims 284-286 and 288 of this application are respectfully requested for the reasons stated above.

If there any questions regarding this Amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 04-1105.

Respectfully submitted,

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